Genetics

Version 5.3

Corrected, Updated, Lighter

PLAB 1 Keys is for PLAB-1 and UKMLA-AKT (Based on the New MLA Content-Map)

With the Most Recent Recalls and the UK Guidelines

ATTENTION: This file will be updated online on our website frequently!

(example: Version 2.7 is more recent than Version 2.6, and so on)

The following table contains a summary of the most commonly asked cases

(Will come across in the following keys in some details)

Autosomal Recessive	Autosomal Dominant	X-Linked Recessive
◙ If **Both** Parents are **Carriers:** • **25%** chance of a child to be **affected**. • **50**% chance of a child to be a **Carrier**. ◙ If one parent is **affected** and the other parent is **carrier** → **50**% chance of a child to be **Affected**. And **50**% chance of a child to be a **Carrier**.	◙ If **One** parent is **Affected** → **50%** chance of a child to be **affected**. → **25%** chance of a Grandchild to be **affected**. **Note**: there is no carrier state of autosomal dominant conditions. If a parent does NOT have the gene → **0%** he will pass to his/her child.	◙ If **Mother** is **Carrier** → **50%** chance of a **Male** child to be **affected**. ◙ If **Father** is affected → **0%** chance of a **Male** child to be **affected**. → **100%** chance of a **Female** child to be **carrier**.
Cystic Fibrosis	Huntington's Disease	Duchenne Muscular Dystrophy (DMD)
Congenital Adrenal Hyperplasia (21-hydroxylase Deficiency).	Neurofibromatosis	Haemophilia
Thalassemia	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	G6PD deficiency

Sickle Cell Anemia	BRCA gene (breast cancer)	
Haemochromatosis	VWD Hereditary spherocytosis	
	Multiple Endocrine Neoplasia (MEN)	

Key 1

Cystic Fibrosis

◘ Understanding the Disease:

Cystic Fibrosis (CF) is caused by **Autosomal Recessive** Mutation in **CFTR gene** "**C**ystic **F**ibrosis **T**ransmembrane Conductance **R**egulator gene". This mutation leads to → Increased Viscosity and Thickness of the body's secretions + High Chloride (Cl^-) in the skin. Think of the symptoms:

- **Salty skin.**

- Thick Secretions and mucous accumulates in the lung "Alveoli" making it a good environment for bacterial infection.

Thus → **Recurrent repetitive cough**, with **sputum**, and **chest infections**.

• Thick secretions, on the long-term, block the pancreatic duct → No pancreatic enzymes are released → ↓ fat and protein Absorption → **Failure to thrive** (**short** and **thin** child) (+) Fat-containing stool, which is called "**Steatorrhea**" which presents with bulky, greasy and offensive smell stools. Also, in the long-term, the pancreas will be damaged → **DM-type 1**.

• In **Males** with CF usually → Congenital Absence of Vas deference → **Infertility**.

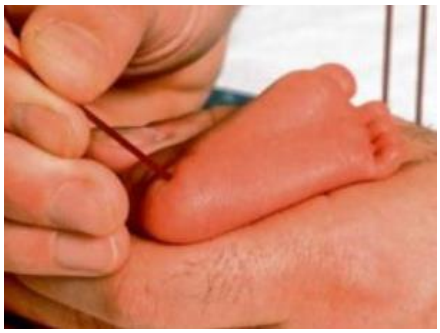
• Early after birth, the meconium "the first stool that is passed by a newborn" might not pass due to thickness → **Meconium ileus**.

In short, the common features of Cystic Fibrosis (CF).

- Salty-tasting skin, which parents notice when they kiss their child
- Frequent coughing, wheezing, or bouts of pneumonia or sinusitis "recurrent chest infections".
- Difficulty breathing that keeps getting worse
- Big appetite but poor weight gain (Failure to Thrive).
- (Steatorrhea) → Bulky, smelly, greasy bowel movements.
- Finger Clubbing.
- **In the long-run [Complications]** →

Diabetes, **Cirrhosis**, **Respiratory failure**, **Bronchiectasis** "widened, dilated airways → more susceptible for sputum and mucous collection and infection.

Diagnosis



◙ In the UK, there is a neonatal screening test for CF → (**Guthrie test**) using **heel-prick test** when the baby is 7-10 days old.

If positive → Confirm by **Sweat test** and Genetic testing for CFTR.

◙ If CF was not diagnosed during neonatal period and it is suspected in an older individual → Perform **Sweat Test** or **Genetic testing for CFTR**.

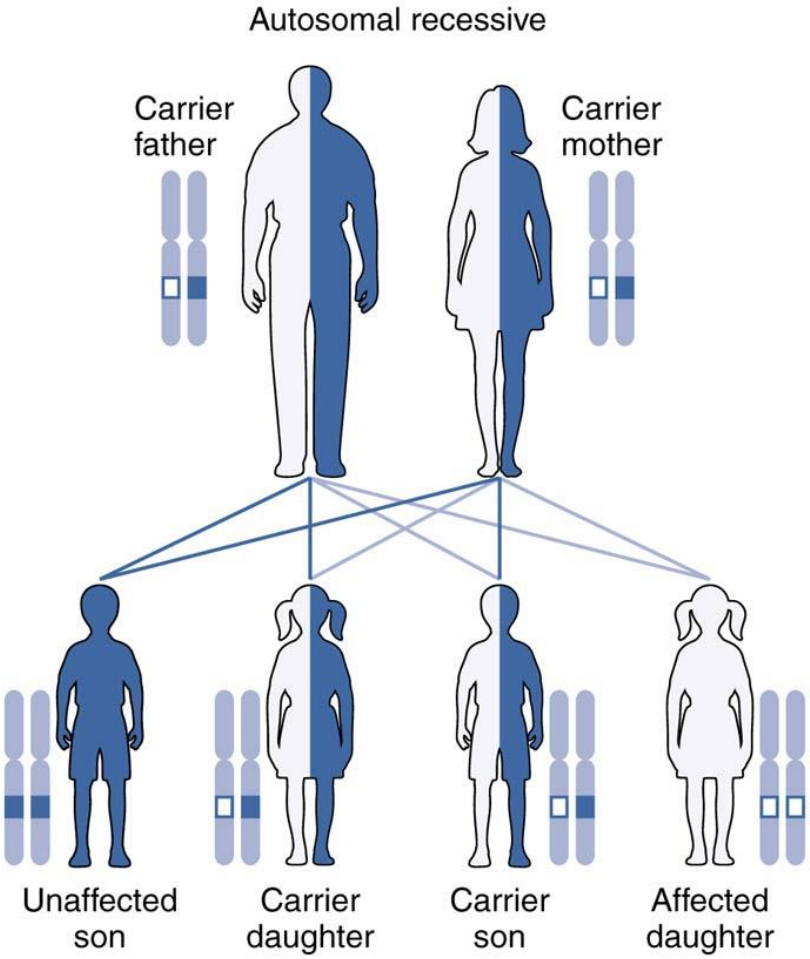
Note:

CF is an **Autosomal Recessive** disease. This means that **if both parents are carriers**, their children will be:

♦ **25%** → **Unaffected** (Completely healthy and do not have the mutated gene).

♦ **25%** → **Affected** (have the disease).

♦ **50%** → **Carriers** (They are carriers but do not have the disease manifested).



Autosomal Recessive Inheritance (Source: Wikimedia)

♣ Other Autosomal Recessive Conditions:

Cystic fibrosis / Thalassemia / Sickle Cell Anemia / Wilson's disease / Congenital Adrenal Hyperplasia (CAH).

Treatment

There is **no cure** for cystic fibrosis, but treatment can ease symptoms and reduce complications.

• Lung infections are treated with antibiotics. Sometimes, the antibiotic **azithromycin** is used long-term.

• Inhaled hypertonic saline and salbutamol may also be useful.

• Lung transplantation may be an option if lung function continues to worsen.

• Pancreatic enzyme replacement and fat-soluble vitamins supplementation are important, especially in the young.

• **Airway clearance techniques such as chest physiotherapy** have some short-term benefit, but long-term effects are unclear.

♠ The average life expectancy is between 42 and 50 years in the developed world. Lung problems are responsible for death in 80% of people with cystic fibrosis.

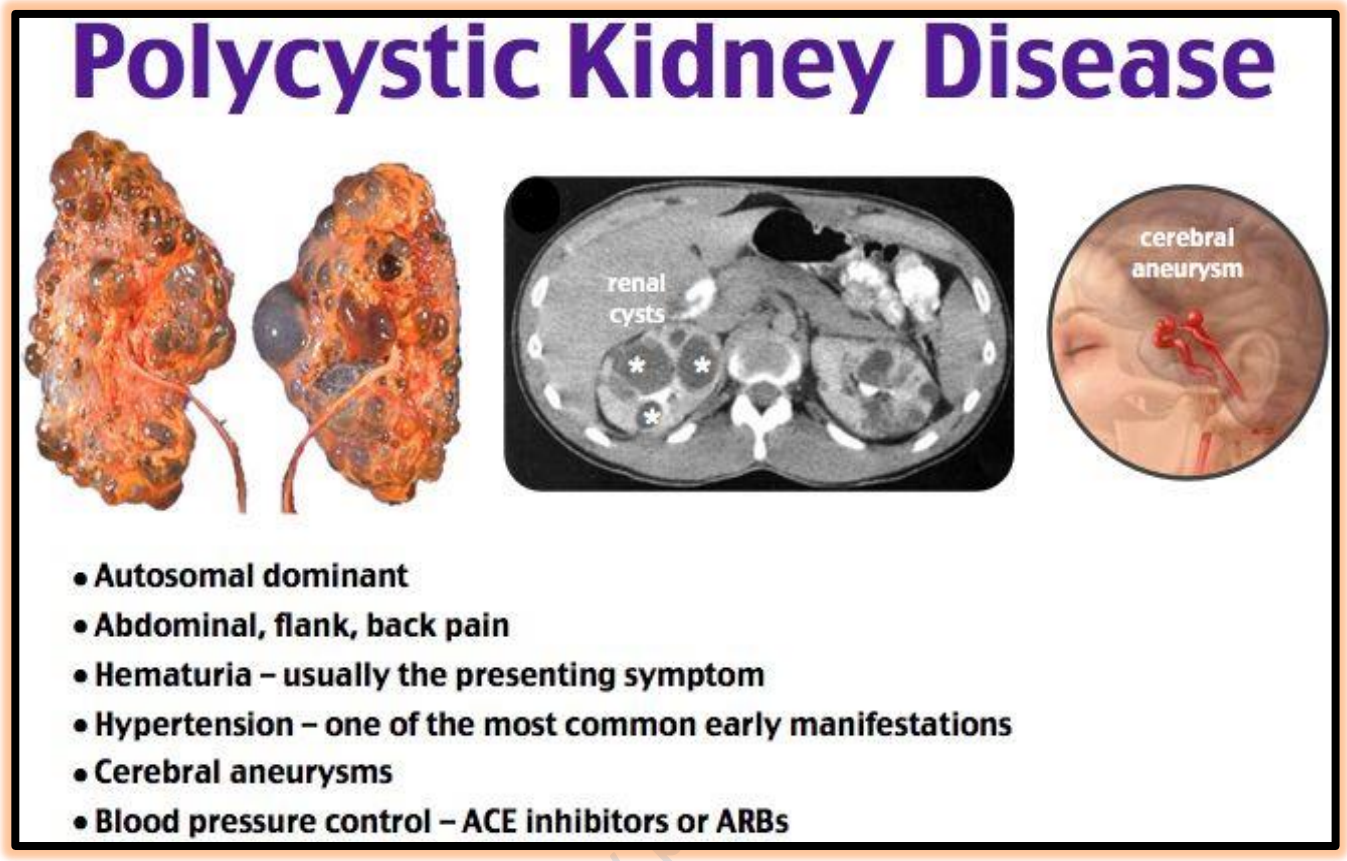
♠ CF is most common among people of Northern European ancestry and affects about one out of every 3,000 newborns.

What do you need to know for the exam?

◙ CF → **Autosomal Recessive**.

- **50**% chance for children to be → **Carriers**.

	- **25**% chance for children to be → **Diseased** (**Affected**). ◙ A child presents with **repetitive cough**, low percentile for weight and height (**Failure to thrive**), **Steatorrhea** (Greasy, bulky and smelly stools that float), rectal prolapse (due to bulky stool), **recurrent chest infections**. → Suspect **Cystic Fibrosis** and perform → chloride **Sweat Test**.
Key 2	**Polycystic Kidney Disease PKD** ◙ **Autosomal Dominant** → **50%** chance for a child to be affected if one parent has the disease. ◙ **Important association that you have to remember is:** **PKD** has an association with **Cerebral Aneurysm** which if ruptures → **Subarachnoid Haemorrhage** develops.



◙ Autosomal **Recessive** Conditions:

Cystic fibrosis ▌Thalassemia ▌Sickle Cell Anemia ▌Wilson's disease ▌Congenital Adrenal Hyperplasia (11/17/21- Hydroxylase Deficiency) ▌Haemochromatosis

◙ Autosomal **Dominant** Conditions:

ADPKD ▌Huntington ▌Neurofibromatosis ▌BRCA genes

Key 3

Quick Notes on Turner's Syndrome (Female 45 XO):

√ It results when one of the X chromosomes (sex chromosomes) is missing or partially missing (45 XO).

√ **Important**: Turner's syndrome is characterised by inability to produce oestrogen. This would ultimately lead to ↑FSH and LH (due to the loss of negative feedback).

A previous question: What are the hormonal changes in Turner syndrome?

→ ↓Oestrogen, ↑FSH and LH.

√ Most ♀ have normal intelligence BUT some **still have learning difficulties**.

√ Human Growth Hormone (**GH**) **is used** during childhood to increase the height (effective and a part of the management).

√ **Oestrogen Replacement Therapy** can be used during **CHILDHOOD** to enhance Breasts and Hips development **and** to prevent Osteoporosis.

√ Advanced age of mother is **NOT** a risk factor for Turner's syndrome.

√ Turner's ♀ are **infertile** (Ovarian Dysgenesis). However, some **can conceive** by the assisted reproductive techniques.

Important Features of Turner's Syndrome:

Short stature | Short Webbed neck | Widely spaced Nipples |

OVARIAN FAILURE (1ry Amenorrhea) | Impaired Pubertal

Growth | Bicuspid Aortic Valve

Example (1),

◙ 12 YO ♀ is short for her age and has extra skin fold on the neck. One important additional feature is → **Ovarian Failure** (1ry Amenorrhea).

Example (2),

◙ 16 YO ♀ with 1ry Amenorrhea, Short stature, Low set of ears, Broad Chest, Widely spaced nipples.

The Likely Dx → **Turner's Syndrome (45 XO)**

Key 4

Prader Willi Syndrome

♦ Genetic/ congenital disease →

Deletion of some genes of the **paternal chromosome #15.**

♦ During **Neonatal** period → **Hypotonia** (**Floppy baby**) / Difficult to feed (thin upper lip and downturned mouth) / short extremities / **almond-shaped eyes**.

♦ During **Childhood** → **Excessive eating** (**hyperphagia**) / **Obese** and **Short** / **learning difficulties** / growth abnormalities / self-injurious behaviour.

♠ *Brother Willi is like an octopus; he is **Floppy** and **likes to eat**!*

Key 5

Duchenne Muscular Dystrophy (DMD)

◙ **X-linked Recessive** → a **Male** child has **50%** risk to **inherit the gene** if his mother is a carrier.

X-linked recessive only affects males.

◙ For the Exam: DMD Criteria:

√ **4-8** YO ♂ (**boy**) who started to walk late (≥ 18 months instead of 12 months).

√ Gower's sign → the boy uses his hands to push on his legs to stand.

√ Proximal Muscle weakness, waste (e.g., bilateral calf hypertrophy).

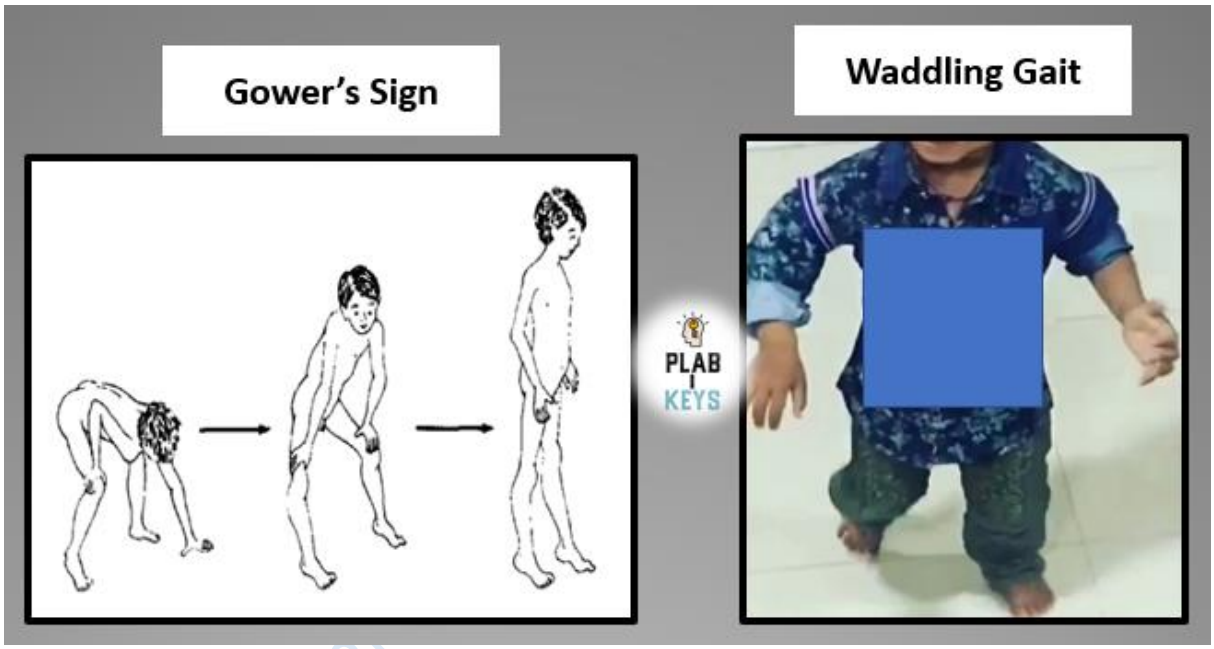
(Delayed or difficult walking, jumping, running, hopping)

√ Reduced deep tendon reflexes.

√ Waddling gait (he cannot run).

√ (↑) CK "Creatine Kinase", ALT, AST.

√ (±) Respiratory and/or Cardiac manifestations.



◙ Diagnosis:

→ **Initial** test → **CK** "Creatine Kinase".

→ **Muscle Biopsy**.

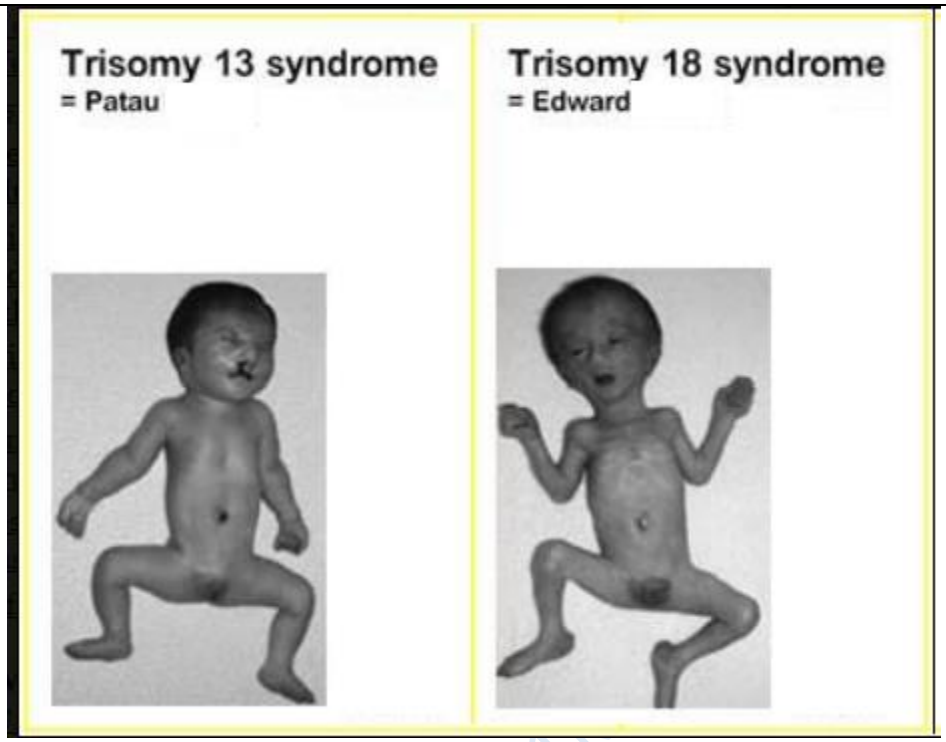
→ **Genetic Testing** (Obligatory after +ve muscle biopsy).

◙ Important Note:

DMD has a mutation defect in **Dystrophin protein** which lies in **Striated muscles**.

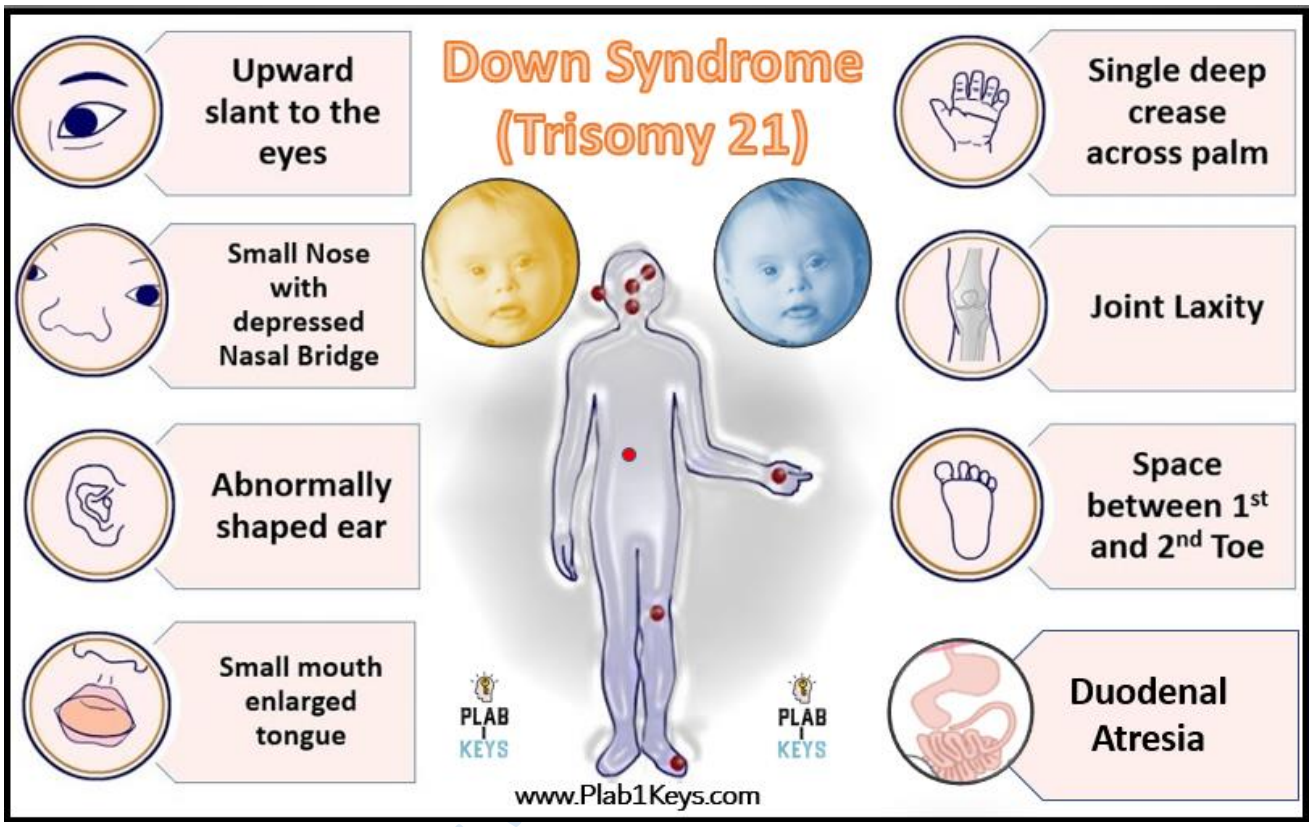
	◙ X-linked **Recessive** Conditions→ **DMD ▌Haemophilia**
Key 6	◙ Autosomal **Recessive** Conditions: (25% if **both parents** are **carriers**) **Cystic fibrosis ▌Thalassemia ▌Sickle Cell Anemia ▌Wilson's disease ▌Congenital Adrenal Hyperplasia (e.g. 21-Hydroxylase Deficiency) ▌Haemochromatosis** Also, in autosomal recessive conditions: **If one parent is** affected **and the other parent is** carrier → 50% chance of a child to be Affected. **And** 50% chance of a child to be a Carrier. ◙ Autosomal **Dominant** Conditions: (50% if **One parent** is **affected**) **ADPKD ▌Huntington ▌Neurofibromatosis ▌BRCA genes in breast Ca** ◙ X-linked **Recessive** Conditions: (**Male**: 50% if **mother** is **carrier**) **DMD ▌Haemophilia**

Key 7



Trisomy 13 (Patau Syndrome)	Trisomy 18 (Edward Syndrome)
Prominent Calcaneus (rocker bottom feet).	Prominent Calcaneus (rocker bottom feet).
Cleft lip and palate.	Prominent Occiput
Microcephaly (Small Head)	Microcephaly (Small Head).
Microphthalmia (Small Eyes)	Micrognathia (Small Jaw).
Polydactyly (Multiple Fingers)	Hands are clenched into fists with Overriding Fingers.

Trisomy 21 (Down Syndrome)



Example,

A neonate's chest x-ray shows "Double Bubble Sign". He has flat occiput and low set of ears.

The likely Dx → **Down Syndrome**.

Note: **Double bubble sign** → **Duodenal Atresia**.

♠ ***Brother "Prader" Willi*** *is like an* ***octopus****; he is* ***Floppy*** *and* ***likes to eat so much****!*

♠ ***Edward*** *has 2 prominents and 2 smalls:*

√ *The 2 prominents are the highest (Occiput) and the Lowest (Calcaneus).*

√ *The 2 smalls are small* ***head*** *and small* ***jaw****. 2X2= 4 (X2) = 8 → Trisomy 18.*

♠ ***Patau*** *→ cleft lip and palate, 2 smalls:* ***head*** *and* ***eyes****. Many fingers (13) → Trisomy 13.*

♦ *Many fingers in* ***Patau*** *(13), fingers override each other in* ***Edward (18)****.*

Example,

32 weeks stillbirth baby → Microcephaly, Micrognathia (small jaw), Prominent Occiput and Prominent Calcaneus.

→ **Edward's Syndrome (Trisomy 18)**.

Key 8	DMD "**Duchenne Muscular Dystrophy**" is **X-linked recessive**. If the **mother is carrier** and the baby is **MALE** → **50%** chance to be affected.
Key 9	**Congenital Adrenal Hyperplasia** ◙ **Autosomal Recessive** (Like ***Cystic Fibrosis***, ***Thalassemia***, ***Sickle Cell Anemia***) → If both parents are carriers → **25%** (**1:4**) chance their child will be affected. ◙ Cortisol Deficiency ± Aldosterone Deficiency ± **Androgen Excess**. ◙ The most common form → **21-Hydroxylase Deficiency** ◙ **Classic Presentation:** • **Female** → Ambiguous genitalia. • **Male** → Penile Enlargement, Hyperpigmentation • **Infant Male** → **Salt Wasting** (due to **Aldosterone Deficiency**) → Vomiting, Weight Loss, Lethargy, Dehydration, ↓Na+, ↑K+ → (**11-ß-Hydroxylase Deficiency**)

◙ Congenital Adrenal Hyperplasia In adults:

• Males → No signs, may be hyperpigmentations (due to ↑ melanocyte-stimulating hormone) "not asked in exam before".

• Females → **Hirsutism** (excessive hair growth in the face, chest, back), **Acne**, **Early pubarche**, **Oligomenorrhea** (due to ↑ 17-hydroxyprogesterone that is converted into androgens; testosterone, androstenedione).

If this is the stem, we request → **17-hydroxyprogesterone**.

Remember that polycystic ovarian syndrome (PCOS) is different:
◙ Inability to conceive (infertility) + Obesity + Acne + ↑ LH
→ **Polycystic ovarian syndrome** PCOS → (do **pelvis ultrasound**)

Key 10

Autosomal Recessive	Autosomal Dominant	X-Linked Recessive
If **Both** Parents are **Carriers** → • **25%** chance of a child to be **affected**. • **50**% chance of a child to be a **Carrier**. ▣ If one parent is **affected** and the other parent is **carrier** → **50**% chance of a child to be **Affected**. And **50**% chance of a child to be a **Carrier**.	If **One** parent is **Affected** → **50%** chance of a child to be **affected**. → **25%** chance of a Grandchild to be **affected**.	If **Mother** is **Carrier** → **50%** chance of a **Male** child to be **affected**.
Cystic Fibrosis	Huntington's Disease	Duchenne Muscular Dystrophy (DMD)
Congenital Adrenal Hyperplasia (21-hydroxylase Deficiency).	Neurofibromatosis	Haemophilia
Thalassemia	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	G6PD deficiency

	Sickle Cell Anemia	BRCA gene (breast cancer)	
	Haemochromatosis	VWD Hereditary spherocytosis	
		Multiple Endocrine Neoplasia (MEN)	

Key 11

Klinefelter Syndrome

Klinefelter Syndrome: 47,XXY males

(**G**- **FELTER**)

• *Gynecomastia* ▌• *Facial hair: low* ▌• *Estrogen is High but testosterone is low* ▌

• *Long limbs* ▌• *Tall, slim* ▌• *Elevated FSH, LH* ▌• *Rage "Aggressive Behaviour"*

√ Low testosterone.

√ High estrogen, FSH, LH.

√ **Hypogonadism** → **Small testes** → **Azoospermia** (no sperms in semen) → male **infertility**.

√ Best Diagnosed by → **Karyotyping** = (**Chromosomal Analysis**) (47 XXY).

Example:

28 YO **Tall** and **Slender** "Thin" man presents with his wife complaining of **inability to conceive**. His semen analysis shows **Azoospermia** "No sperms in the semen". O/E, His **testes** are **small** and firm.

- The likely Diagnosis → **Klinefelter's Syndrome (male 47 XXY).**
- The Investigation to diagnose him → **Karyotyping = Chromosomal Analysis**.

Tall, Thin boy, (Spontaneous Pneumothorax), long extremities, scoliosis, flexible joints, Myopia

→ **Marfan's Syndrome**

(spontaneous pneumothorax is common in Marfan's Syndrome)

Do not mix thing up with **Klinefelter's Syndrome** as it appears in Adulthood.

Absent Thymic shadow → **DiGeorge Syndrome**.

Key 12	A middle-aged woman presents with Progressive Cognitive Impairment "memory loss, poor concentration, inability to recognise objects" and Chorea "repetitive involuntary writhing movement of a limb" → **Huntington's Disease (HD)** • **Autosomal Dominant** "if one parent is affected → 50% chance for a child to be affected". • Early signs → changes of personality, self-neglect, clumsiness. • **Progressive Cognitive Impairment** "memory loss, poor concentration…etc". • Later → **Chorea** "involuntary writhing -jerky- movement of a limb". Dystonia, Rigidity, Dementia. **Cognitive impairment + Jerky involuntary movements + FHx → Huntington's.** **Example,** An elderly man presents with Hx of changes in his mood and personality over the last year which were followed by poor memory and concentration. Then, he developed progressive fidgety movements and **choreiform** movements. He has 3 adult children (25, 28, 31 YO). His oldest son has recently started to show erratic personality and fidgety restless movements of his lower limbs.

→ **Huntington's Disease**

→ **Autosomal Dominant with ANTICIPATION**.

Anticipation = the symptoms in the next generations appear earlier and earlier.

Key 13

Investigating Potential Genetic Diseases

◙ **Before Pregnancy** → **Pre-implantation Genetic Diagnosis (PGD)**

√ Fertilisation is done in vitro "in the laboratory" → The embryos are then tested for genetic abnormalities → 1 or 2 unaffected embryos are then implanted into the uterus.

√ Suitable for possible serious genetic disease such as Cystic Fibrosis and Sickle Cell Anemia when there is a strong FHx or a parent is carrier.

◙ **Week 11-14 of pregnancy** → **Chorionic Villous Sampling (CVS).**

√ A small sample of the placenta is tested.

◙ **Week 15-20 of pregnancy** → **Amniocentesis.**

√ A small sample of the amniotic fluid is tested.

	Example, A woman is planning to get pregnant soon but she is afraid as she has FHx of Cystic Fibrosis. What is the earliest possible investigation? → **Preimplantation Genetic Diagnosis (PGD)**
Key 14	*Hyperelasticity of skin* + *Hypermobility of joints* ± *Blue Sclera* → EDS "**Ehlers-Danlos Syndrome**" (Collagen Problems).
Key 15	**Neurofibromatosis (NF)** √ **Autosomal Dominant** → If one parent is affected → 50% chance of a child to be affected. **√ Diagnostic criteria for Neurofibromatosis**

- 6 or more café au lait macules (>0.5 cm in children or > 1.5 cm in adults)
- 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
- Axillary or groin freckling
- Optic pathway glioma
- 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
- Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/- pseudarthrosis)
- First degree relative with NF1

◙ **NF type 1** presents more with **skin lesions. (e.g. Café-au-lait spots/ Axillary or Groin Freckles/ iris hamartomas/ scoliosis / association with Pheochromocytoma).**

◙ **NF type 2** presents more with **CNS tumours**. **(e.g. Bilateral acoustic neuroma / multiple intracranial schwannomas, meningiomas)**

Example,

A pregnant 31 YO ♀ has bilateral cerebellopontine tumours, bilateral SNHL and multiple café-au-laits spots. What is the possibility that her coming baby to be affected of the same condition as his/her mother?

→ **1:2 (50%)**

"The mother likely has Neurofibromatosis which is Autosomal Dominant"

Key 16	**A woman with Strong FHx (1st or 2nd degree History) of ovarian cancer.** √ Do → **pelvic U/S** √ If unremarkable → **Genetic Counselling** "for full assessment of risk" √ If High Risk → Offer **Prophylactic Salpingo-oophorectomy**. ◙ If there are manifestations of ovarian Cancer → **U/S** + **CA-125 level.** **Example,** A 40 YO ♀ has her two sisters diagnosed with Ovarian Carcinoma. She has done pelvic U/S which was unremarkable. What is the next step? → **Genetic Counselling**.
Key 17	A pregnant woman on her 16-week-gestation wants to make sure that her unborn baby does not have Down Syndrome. What is the most definitive investigation? → **Amniocentesis**. **Remember:** ◙ **Before pregnancy → Preimplantation Genetic Diagnosis (PGD).**

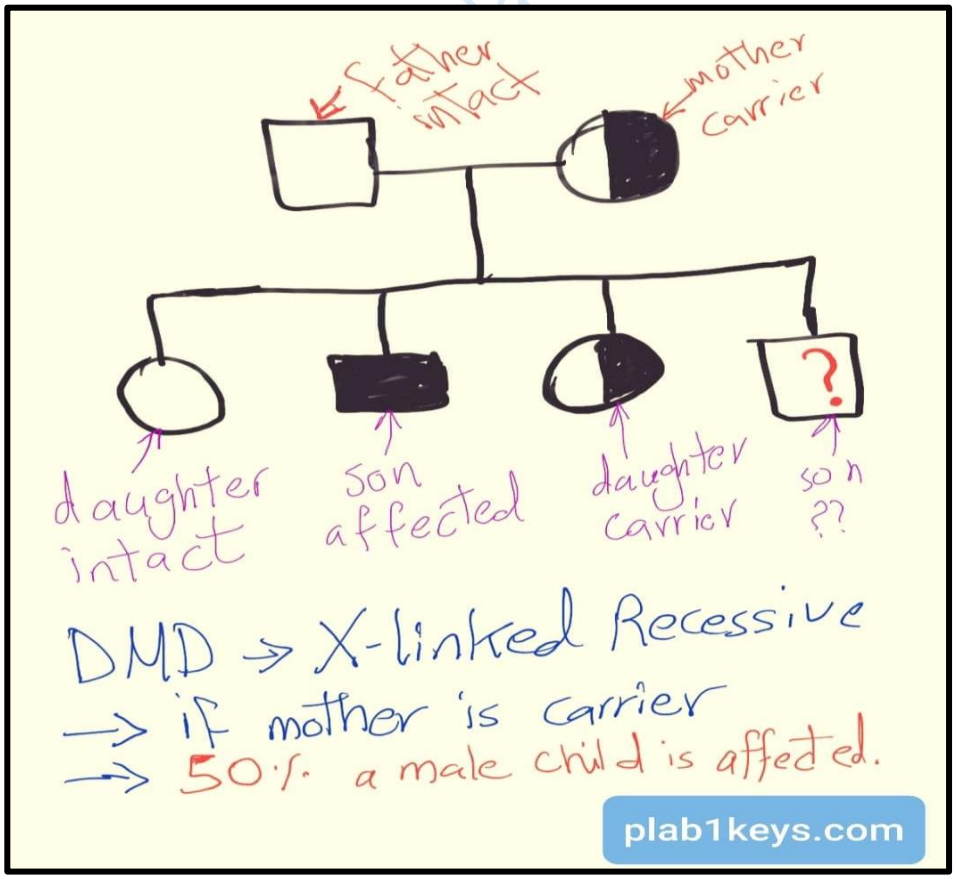
	◙ **11-14 Week gestation** → **Chorionic Villous Sampling.** ◙ **15-20 Week gestation** → **Amniocentesis.**
Key 18	**Scenario:** 2 healthy parents have one child with cystic fibrosis and another healthy child. What is the chance for the 3rd child to be a **Carrier**? CF is **Autosomal Recessive** → If both parents are carriers, the children's chances are as follow: • 25% (1:4) → Healthy • 25% (1:4) → Affected • 50% (1:2) → Carrier Pay attention that the question asks about the chance of being CARRIER not AFFECTED. Thus, **the answer is → 50% (1:2)**

	Note, here, both parents are carriers. This is because they appear "healthy" but they still have a child who has Cystic Fibrosis. This means they are carriers.
Key 19	Q) If a father has Alport syndrome. What is the chance that his "male" son being affected? Answer → **Nearly 0%** Alport's syndrome is **X-Linked disease.** The father will pass "**Y**" Chromosome to his **son** "**Male child**" **not** the affected "**X**" chromosome. Therefore, fathers with X-linked diseases **CANNOT** pass their disease to their Sons! (0%) **Alport syndrome is a genetic condition characterized by:** √ kidney disease: hematuria, proteinuria → End-stage renal disease (ESRD). √ hearing loss: (SNHL) √ eye abnormalities.
Key 20	**Important:**

	For an Autosomal Dominant disease (e.g. Huntington, Neurofibromatosis, ADPKD), if one parent is affected → **50%** of a **child** "First generation" to be affected. → **25%** of a **grandchild** "Second generation" to be **affected**. In one exam they asked what the chance of the grandson to be "a **carrier**"? The answer is (0%) as Huntington's disease is autosomal dominant with complete penetrance; the person is either affected or unaffected; there is no carrier state!
Key 21	◙ The strongest **genetic** risk factor for **Alzheimer's** disease (AD) is: → **APOE ε4 gene** Apolipoprotein E gene (APOE e4 allele)
Key 22	**If a father has Alport syndrome. What is the chance that his "male" son being affected?** Answer → **Nearly 0%**

	Alport's syndrome is **X-Linked disease.** The father will pass "**Y**" Chromosome to his **son** "**Male child**" **not** the affected "**X**" chromosome. Therefore, fathers with **X-linked** diseases **CANNOT** pass their disease to their **Sons**! (0%)
	If a father has Duchenne Muscular Dystrophy (DMD). What is the chance that his "male" son being affected? Answer → **Nearly 0%** DMD is **X-Linked Recessive disease.** The father will pass "**Y**" Chromosome to his **son** "**Male child**" **not** the affected "**X**" chromosome. Therefore, fathers with **X-linked** diseases **CANNOT** pass their disease to their **Sons**! (0%)
Key 23	**A child with cystic fibrosis. What is the chance that his brother will also be affected if both parents are carriers?**

	→ **1:4 (25%)** CF is an **Autosomal Recessive** disease. This means that **if both parents are carriers**, their children will be: ♦ **25%** → **Unaffected** (Completely healthy and do not have the mutated gene). ♦ **25%** → **Affected** (have the disease). ♦ **50%** → **Carriers** (They are carriers but do not have the disease).
Key 24	**If both parents are carriers of congenital adrenal hyperplasia. What is the chance that their coming child to be affected?** → **1:4 (25%)** **CAH is Autosomal Recessive** (Like ***Cystic Fibrosis***, ***Thalassemia***, ***Sickle Cell Anemia***) → If both parents are carriers → **25%** (**1:4**) chance their child will be **Affected**. → If both parents are carriers → **50%** (**1:2**) chance their child will be **Carrier**. ◙ **Also in autosomal recessive conditions:** **If one parent is** affected **and the other parent is** carrier → 50% chance of a child to be Affected. **And** 50% chance of a child to be a Carrier.

Key 25	**A lady who has short stature complains of Primary Amenorrhea (did not have amenorrhea before).** → **Turner Syndrome**.
Key 26	**From the pedigree below, what is the chance of the unborn male baby to be affected by Duchenne muscular dystrophy (DMD)?** 

→ **1:2 (50%).**

Duchenne muscular dystrophy is an X-linked recessive disease.

If the mother is carrier → **50%** chance that her **male** children will be affected.

Autosomal Recessive	Autosomal Dominant	X-Linked Recessive
If **Both** Parents are **Carriers** → • **25%** chance of a child to be **affected**. • **50**% chance of a child to be a **Carrier**. ▣ If one parent is **affected** and the other parent is **carrier** → **50**% chance of a child to be **Affected**. And **50**% chance of a child to be a **Carrier**.	If **One** parent is **Affected** → **50%** chance of a child to be **affected**. → **25%** chance of a Grandchild to be **affected**.	If **Mother** is **Carrier** → **50%** chance of a **Male** child to be **affected**.

Cystic Fibrosis	Huntington's Disease	Duchenne Muscular Dystrophy (DMD)
Congenital Adrenal Hyperplasia (21-hydroxylase Deficiency).	Neurofibromatosis	Haemophilia
Thalassemia	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	G6PD deficiency
Sickle Cell Anemia	BRCA gene (breast cancer)	
Haemochromatosis	VWD Hereditary spherocytosis	
	Multiple Endocrine Neoplasia (MEN)	

Key 27	**Previous PLAB-1 Exam Genetics questions**

◙ A father has Becker muscular dystrophy [X-linked recessive disease]. He has 2 sons and 2 daughters. Who will be affected and who will not be affected?

The father is affected (**x**Y). The small x is (x-linked recessive).

The father will pass (Y) to his "Sons"; therefore, the sons will neither be affected nor carriers. "They will take Y from their father whose **x** is affected".

As for the 2 daughters, each of them will take the affected **x** from the father and another "Healthy" X from their mother. So, both daughters will just be carriers.

The answer is:

→ **2 sons are completely Healthy and 2 daughters are Carriers**.

---

2 parents are carriers of Congenital Adrenal Hyperplasia. What is the possibility of their child being affected?

CAH is an Autosomal Recessive disease.

→ **1:4** (25%) a child will be **affected**.

→ **1:2** (50%) a child will be **carrier**.

Q) If a father has Alport syndrome. What is the chance that his "male" son being affected?

Answer) → **Nearly 0%**

Alport's syndrome is **X-Linked disease.**

The father will pass "**Y**" Chromosome to his **son** "**Male child**" **not** the affected "**X**" chromosome.

Therefore, fathers with **X-linked** diseases **CANNOT** pass their disease to their **Sons**! (0%)

Key 28

◙ The Mode of inheritance of **BRCA** (in breast cancer)

→ **Autosomal Dominant**

	If a family has widespread breast cancer **Think** → **BRCA gene mutation** (either BRCA 1 or BRCA 2 mutation, both can cause breast cancer). **BRCA genes are inherited as autosomal dominant.** **Important:** In addition to **breast** cancer in women, if men are also involved with breast and or or **prostate** cancer → **BRCA 2** mutation is more likely than BRCA 1. BRCA 1 → 1 organ → Breast. BRCA 2 → 2 organs → Breast + Prostate ▌or breast only but men involved.
Key 29	◙ All forms of congenital adrenal hyperplasia (CAH) are inherited in an → **autosomal recessive** manner. If both parents are carrier → **1:4 chance their child will be affected**.
Key 30	**14-year-old boy with short stature. His father says (talking about himself) that he was also the shortest in his class till he was 15 years. Growth is at the 9th centile, growth velocity is 6cm/yr. other examination findings are normal. What is the most appropriate approach to evaluate short stature?**

A) Endomysial antibodies status

B) MRI

C) review in 6 months

D) TFT

E) **wrist X-ray for bone age**

Constitutional Delay in Growth and Puberty.

◙ Some children have delayed puberty, short stature (skeletal and height growth -Temporarily- ceases). They stop in growth at 10-12 YO , and then they may start gaining length again to catch their peers at 17 YO.

◙ There is usually FHx of similar growth pattern.

◙ What investigation should be done in this case?

→ **X-ray of the left hand and wrist.**

This is done to obtain the **age of the bone**; how much time has left before fusion of the gaps between bones and stopping of growth, is there an indication to give GH?

The next step would accordingly be made but it is mostly → **Reassurance**.

Key 31	Young boy with Duchenne's muscular dystrophy. Parents want to know the chances of their second male child being affected. a) 25% b) **50%** c) 100% d) 75% e) 0% **DMD → X-liked Recessive**. He is a boy with X linked disease. This means that he has inherited the condition from his mother. (Remember, the father cannot pass x linked condition to his SON). Knowing that his mother is the affected party, there is 50% chance that their coming child to be affected (she will give him one of her 2 X chromosomes). Even if the coming baby is a female, she will take a normal x from her father, and the other x is from her mother. The mother has 2 Xs, one is normal and the other is not. So, there is a **50% chance** of a baby (either male or female) to inherit that faulty x from the mother.

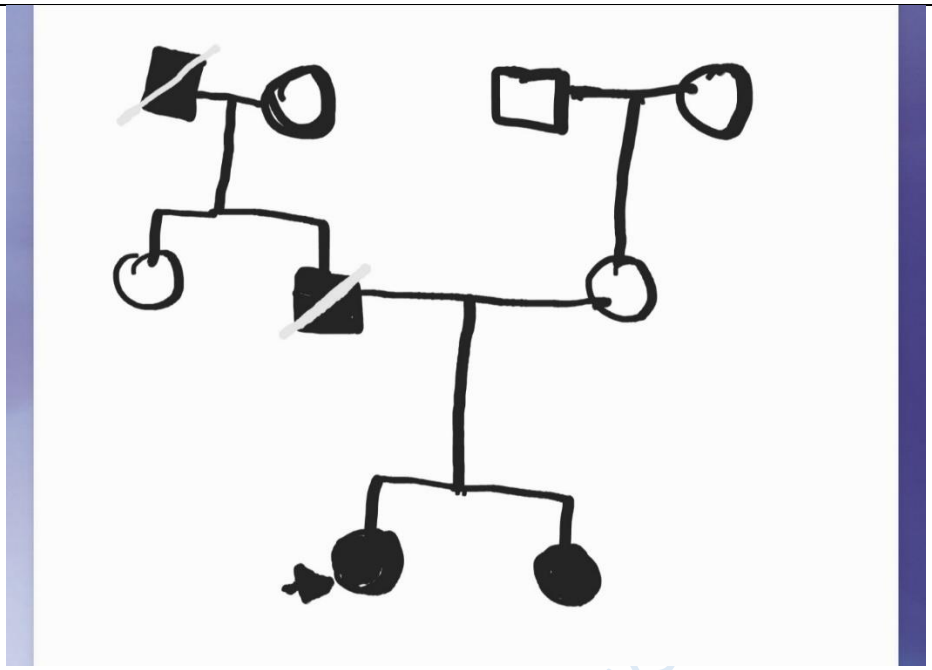
Key 32	**A woman with features suggestive of neurofibromatosis (cafe au lait spots….) wanted to know the risk of her child being affected.** A. 1 in 4 B. 1 in 8 C. **1 in 2** D. 100% **NF is Autosomal Dominant → 1:2 (50%) chance of a child being affected.**
Key 33	**A pregnant Sickle cell trait patient found out her partner is also sickle cell trait. She wants to know the chances of her unborn child having SCD.** A. 0% B. **25%** C. 50% D. 100% SCD is autosomal recessive, if parents are carriers → 25% If one parent diseased and the other is carrier → 50%

	Sickle cell trait patients have 1 normal gene and one sickle gene While sickle cell anemia patients have both genes diseased. --- **◙ A Quick Recap from the haematology chapter:** √ **Hemophilia** → X-linked Recessive. √ **G6PD deficiency** → X-linked Recessive. √ **VWD** → Mostly Autosomal Dominant. √ **Hereditary Spherocytosis** → Mostly Autosomal Dominant. √ **Thalassemia** → Autosomal Recessive. √ **Sickle Cell Anemia** → Autosomal Recessive. ◙ Autosomal **Recessive** Conditions: (25% if **both parents** are **carriers**) ◙ Autosomal **Dominant** Conditions: (50% if **One parent** is **affected**) ◙ X-linked **Recessive** Conditions: (**Male**: 50% if **mother** is **carrier**)
Key 34	**Notes on Autosomal Dominant Conditions:** √ **Neurofibromatosis type** 1 → Autosomal dominant with complete penetrance.

	√ **BRCA 1 gene mutation** → Autosomal dominant with Incomplete penetrance. Incomplete penetrance = 80% of those having the mutation will develop breast cancer "incomplete = not 100%". √ **Huntington's** → Autosomal dominant with anticipation and complete penetrance. • Anticipation = the condition will appear in earlier ages with generations. e.g., first generation will develop it at 60 years of ages 2nd generation will develop it at 45 years of age, and so on. (Example only). • Complete penetrance = 100% of those having the mutation will eventually develop the disease "the disease will become manifested on them".
Key 35	**If a mother carries the X-linked recessive gene (e.g. DMD):** ♦ 50% of **MALE** children will be DISEASED. ♦ 50% of **Female** children will be CARRIERS. **If a father carries the X-linked recessive gene (e.g. BMD):**

	♦ 0% of **MALE** children will be DISEASED. ♦ 100% of **Female** children will be CARRIERS.
Key 36	**Fragile X-syndrome is an X-linked Dominant condition.** ◙ **If the mother is affected:** → 50% of children "either male or female" will have the faulty gene. ◙ **If the father is affected:** → 0% of the **male** children will be affected (they take Y from their father, not X). → 100% of the **female** children will have the faulty gene.
Key 37	**Haemophilia A is an X-linked recessive condition. If the mother is a carrier, there a 50% chance that her "male" baby to be affected.**
Key 38	**A 28-year-old pregnant woman.** **She is primigravida (first-time pregnant).** **As a child, she developed hemolytic disease of the newborn.** **She is the second born in her family "i.e., she has an elder sibling".** **Her blood group is O -ve, and her husband is O -ve as well.**

	◙ **What is the chance that her unborn child to have hemolytic disease of the newborn?** • This pregnant mother has likely developed hemolytic disease as a newborn because her elder sibling was Rh +ve, and her mother was Rh -ve. This had sensitised their mother (made their mother to develop Anti-D antibodies). • Since this pregnant woman in stem is Rh -ve, the anti-D antibodies in the blood of her mother had attacked her blood when she was fetus and caused her hemolytic disease of the newborn. **Back to the present time:** • This is her first pregnancy, i.e., not sensitised yet, i.e., no anti-D antibodies in her circulation. • Also, both parents are O -ve, so their child will be O -ve as well. → No ABO or RH incompatibility is likely. In addition, hemolytic disease of the newborn is **not** a genetic condition. **Thus, the answer is →** **0%**
Key 39	**What is the mode of inheritance shown in the following pedigree?**



- **Square** = Male.
- **Circle** = Female.
- **Shaded squares or circles** = affected individuals.
- **Half-shaded squares or circles** = carriers.
- **The line that crosses over a square or a circle** = dead "deceased".
- **The arrow** = the person who attended the clinic to seek information about his genetic condition "Proband = the starting point of the genetic study".

The pattern shown here is

→ **Autosomal dominant**

Key 40

A grandfather has Huntington's disease. What is the chance his grandson would be a carrier?

The answer is (0%) as **Huntington's** disease is autosomal dominant with complete penetrance; which means the person is either **affected** or **unaffected**; there is no **carrier** state! Be careful of the words of the questions.

• If it asked about the chances of his **son** to be **affected**, the answer would be **50**%.

• If it asked about the chances of his grandson to be affected, the answer would be 25%.

• If it asked about the chances of his grandson to be unaffected, the answer would be 75%.

(All had been asked previously).

A grandfather with **Huntington's Disease** (**Autosomal Dominant** with anticipation & complete penetrance ie, no carrier, either affected or unaffected)

Anticipation = The condition will appear in earlier ages with each generation.

Complete penetrance = 100% of those having the mutation will eventually develop the disease "the disease will become manifested on them".

The chance of his	son	To be affected	50%
The chance of his	son	To be unaffected	50%

The chance of his	son	To be carrier	0%
The chance of his	grandson	To be affected	25%
The chance of his	grandson	To be unaffected	75%
The chance of his	grandson	To be carrier	0%

Huntington's Disease Features:

- Early signs → changes of personality, self-neglect, clumsiness.
- **Progressive Cognitive Impairment** "memory loss, poor concentration…etc".
- Later → **Chorea** "involuntary writhing -jerky- movement of a limb". Dystonia, Rigidity, Dementia.

Cognitive impairment + Jerky involuntary movements + FHx → Huntington's.

Key 41

A grandfather has Huntington's disease. What is the chance his grandson would be unaffected?

The answer is (75%)

See the next key

Key 42

A grandfather with **Huntington's Disease** (**Autosomal Dominant** with anticipation & complete penetrance ie, no carrier, either affected or unaffected)

Anticipation = The condition will appear in earlier ages with each generation.

Complete penetrance = 100% of those having the mutation will eventually develop the disease "the disease will become manifested on them".

The chance of his	son	To be affected	50%
The chance of his	son	To be unaffected	50%
The chance of his	son	To be carrier	0%
The chance of his	grandson	To be affected	25%
The chance of his	grandson	To be unaffected	75%
The chance of his	grandson	To be carrier	0%

Huntington's Disease Features:

- Early signs → changes of personality, self-neglect, clumsiness.
- **Progressive Cognitive Impairment** "memory loss, poor concentration…etc".
- Later → **Chorea** "involuntary writhing -jerky- movement of a limb". Dystonia, Rigidity, Dementia.

Cognitive impairment + Jerky involuntary movements + FHx → Huntington's.

Key 43

Both parents are carriers of hemochromatosis. What is the possibility of their future children developing hemochromatosis?

As **haemochromatosis** is autosomal recessive and both parents are carriers

- The future children becoming **affected** → **25**%.

	• The future children are **healthy** → **25**%. • The future children becoming **carriers** → **50**%. Take care to question words. Here, it asks about the future children developing hemochromatosis (ie, becoming affected, not carriers). So, the answer here is 25% (or 1:4).
Key 44	**A boy (usually 4-8 years old) + Delayed walking + Difficult hopping and running + reduced deep tendon reflexes** **Think →** **Duchenne muscular dystrophy (DMD) (X-linked recessive).**
Key 45	**Examples on Sickle Cell Disease Genetics:** **Scenario (1)** **The mother has sickle cell anemia.** **The father has sickle cell trait.** **What is the chance their child be affected?** ◙ Sickle cell anemia is autosomal recessive. • One parent is affected here with sickle cell **anemia** (ie, both genes are diseased -sickled-: HbS, HbS).

• The other parent has Sickle cell **trait**, which is treated in genetics is like a carrier status (one normal gene HbA, and one sickle gene HbS).

So, in autosomal recessive diseases:

• If one parent is affected and the other parent is normal (not diseased nor carrier)

→ 100% of a child to be a carrier.

• If one parent is affected, and the other parent is carrier (or having sickle cell trait)

→ 50% chance their child will be affected, 50% will be carrier.

• If both parents are carriers → 25% chance of a child to be affected, 50% chance of a child to be a carrier.

So, the answer here → **50%** chance of their child to be affected.

Important autosomal recessive conditions:

Cystic Fibrosis, Congenital Adrenal Hyperplasia (21-hydroxylase Deficiency),

Thalassemia, Sickle Cell Anemia, Haemochromatosis.

Scenario (2)

	The mother has sickle cell trait. **The father has sickle cell trait.** **What is the chance their child be affected?** Sickle cell trait is treated as carrier status in genetics because the affected patient has one normal gene and one sickle gene. Therefore, we can consider that both parents are carriers of the sickle gene → **25%** chance their child will be **affected** And 50% chance their child will be carrier.
Key 46	**Example on Beta-Thalassemia Genetics:** **If both father and mother have beta-thalassemia trait (careful, not sickle cell), what is the probability that their baby will be affected by beta-thalassemia?** → **Female 25%, Male 25%**. **Remember:** Thalassemia is **autosomal recessive**. (So, the baby's gender is not important; it is not X-linked condition).

◙ **If Both Parents are Carriers (or both have b-thalassemia trait-minor-):**

- **25%** chance of a child to be **affected** (either male or female).
- **50%** chance of a child to be a **Carrier** (either male or female).

◙ **If one parent is affected and the other parent is carrier**:

50% chance of a child to be **Affected**.

50% chance of a child to be a **Carrier**.

Important:

We deal with beta thalassemia "trait" or "minor" as a carrier, not affected.

So, consider these parents are carriers of beta-thalassemia, this give 25% of their children to be affected (either males or females).

Elaboration on this:

In beta-thalassemia **trait** (**minor**), one faulty beta-globin gene is inherited. So, the other healthy gene would compensate → no symptoms.

In beta-thalassemia **major**, 2 faulty beta-globin genes are inherited.

Key 47

Example on Haemophilia Genetics:

Example (1)

A father has hemophilia B. The mother is free. What is the probability that their unborn **MALE** baby to be affected with hemophilia B?

→ **0%** (other valid answer → **<1%**)

Haemophilia is X-linked recessive. This means that the father who has hemophilia, his X chromosome is faulty, he will give this faulty X gene to his daughter but not for his son. His son will inherit the Y from his father. So, the answer is → <1%.

Example (2)

A mother is a carrier of hemophilia B. The father is free. What is the probability that their unborn **MALE** baby to be affected with hemophilia B?

→ **50%**.

He will take the Y from his father.

He will take of the 2 Xs from his mother.

He has a chance either to take the healthy x or the faulty X from his mother,

Thus → 50%.

In X-linked recessive condition (eg, hemophilia, DMD, G6PD deficiency).

- If **Mother** is **Carrier**

→ **50%** chance of a **Male** child to be **affected**.

- If **Father** is affected

→ **0%** chance of a **Male** child to be **affected**.

→ **100%** chance of a **Female** child to be **carrier.**

Key 48

Wilson's Disease.

♦ Autosomal Recessive.

♦ **Copper deposition in Liver**.

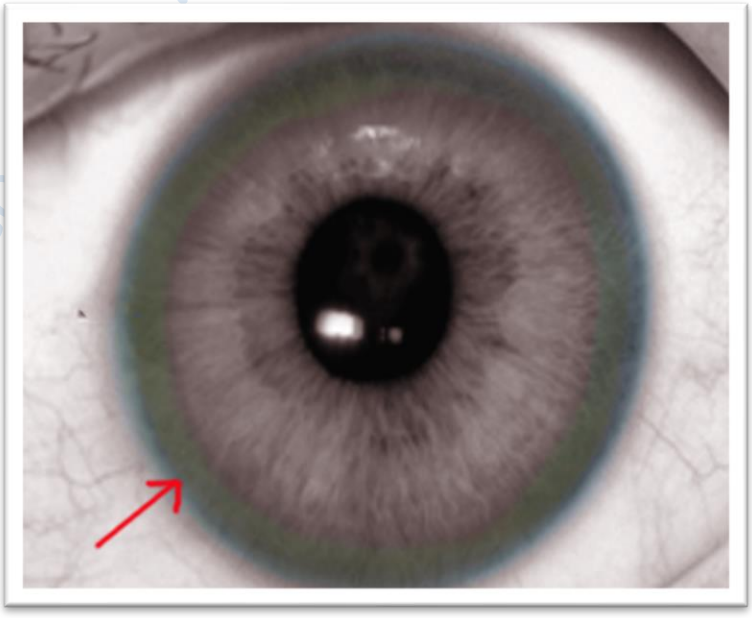
♦ Presentation

√ **Liver problems** → Hepatosplenomegaly, Deranged Liver function, Cirrhosis.

√ **CNS** → Ataxia, Asymmetrical tremor, Dysarthria, Dystonia (Clincher √).

√ **Behavioural** → Decrease school performance, Personality changes (√)

√ **Kayser–Fleischer rings** (**KF rings**) are dark rings that appear to encircle the cornea of the eye. They are due to **copper** deposition in the Descemet's membrane seen in Wilson's disease. (important √).



Greenish-gold ring on cornea (due to **copper deposition**)

This is called **Kayser-Fleisher ring**, seen in **Wilson's disease**.

♦ Dx of Wilson's disease:

√ Initially → LFT (+) Serum Ceruloplasmin (very low < 0.1)

♦ Rx of Wilson's disease:

√ Lifelong penicillamine.

√ If Acute Liver Failure → Liver Transplant.

Hereditary Haemochromatosis.

♦ Autosomal Recessive.

♦ ↑ intestinal Absorption of Iron ⟶ **Iron Accumulation "Deposition"** in Tissues, such as:

· **Liver** "The main organ of iron deposition" ⟶ **Hepatomegaly**, **Cirrhosis** ⟶ HCC = **Hepatoma** "Hepatic Cancer" .

· **Pancreas** ⟶ **Diabetes Mellitus**.

· **Skin** ⟶ **Bronze Skin** (**Hyperpigmentation**).

· **Joints** ⟶ **Arthropathy**.

· **Heart** ⟶ Arrhythmia, **Cardiomyopathy** ⟶ **Dyspnea**.

	♠ Remember in Haemochromatosis: → the **TRIAD**: **Hepatomegaly** + **DM** + **Bronze Skin** ± **Arthropathy.** ♠ Remember that the "**Liver**" is the most likely organ to get **cancer** in Haemochromatosis (Due to Cirrhosis and iron deposition). ♠ Remember that **Wilson's** has ***CNS*** and ***Behavioural issues***! (clincher √)
Key 49	**If a Family has Widespread Breast Cancer:** • **Think** → **BRCA gene mutation** (either BRCA 1 or BRCA 2 mutation, both can cause breast cancer). • **BRCA genes are inherited as autosomal dominant.** • **Important:** In addition to **breast** cancer in women, if **men** are also involved with breast and or **prostate** cancer → **BRCA 2** mutation is more likely than BRCA 1.
Key 50	**Important Genetic Association to Remember for the Exam** • **HLA-DQ2** → Celiac disease + Type 1 Diabetes mellitus.

- **HLA-DQ3** → Type 1 Diabetes mellitus.
- **HLA-DQ8** → Celiac disease, Rheumatoid arthritis, and Juvenile diabetes.

I ate (8) too (2) much **gluten** at **D**airy **Q**ueen

→ HLA-**DQ8** and HLA-**DQ2** linked to **Celiac disease** (**gluten**).

- **HLA-B27** → Ankylosing spondylitis, Psoriatic arthritis, Reactive arthritis, Inflammatory bowel disease.
- **BRCA (1 or 2)** → Breast cancer.
- **BRCA 2** → Breast cancer in woman + Prostate/ Breast cancer in men.
- **APOE ε4 gene** = Apolipoprotein E gene (APOE e4 allele) → Alzheimer's.

Previous Questions on this:

Q1)

A 46-year-old man has recently been diagnosed with invasive breast cancer. His father has a history of prostate cancer, and his 2 sisters have breast cancer. What is the most likely gene affected?

→ BRCA 2 gene.

Q2)

What is the strongest genetic risk factor for Alzheimer's disease (AD)?

→ APOE ε4 = Apolipoprotein E gene (APOE e4 allele).

Q3)

An 8-year-old boy has recently been diagnosed with celiac disease and type 1 diabetes mellitus. What is the most likely associated gene?

→ HLA-DQ2 gene.

(**DQ**: Drama Queen 😅 | **2**, for 2 diseases (DM, Celiac).

Key 51

Regarding Autosomal Dominant Conditions:

Q) A 72-year-old man has Huntington's disease. His daughter tested negative for Huntington's disease gene (ie, she does not have the gene). What is the likelihood that her child will develop Huntington's disease?

Answer → 0%.

- Huntington's disease is autosomal dominant with complete penetrance.
- There is no carrier state of this disease.
- It is either they have the gene (50% that they will pass it to their child) or they do not have the gene (0% they will pass it).

Be careful to the question wording. See the following 2 questions:

Q) A 72-year-old man has Huntington's disease. What is the likelihood that her child will develop Huntington's disease?

Answer → 50%.

Q) A 72-year-old man has Huntington's disease. What is the likelihood that her grandchild will develop Huntington's disease?

Answer → 25%.

Remember: Regrading Autosomal Dominant Conditions:

◙ If One parent is Affected

→ **50**% chance of a child to be affected.

→ **25**% chance of a Grandchild to be affected.

◙ Note: there is no carrier state of autosomal dominant conditions. If a parent does NOT have the gene → **0**% he will pass to his/her child.

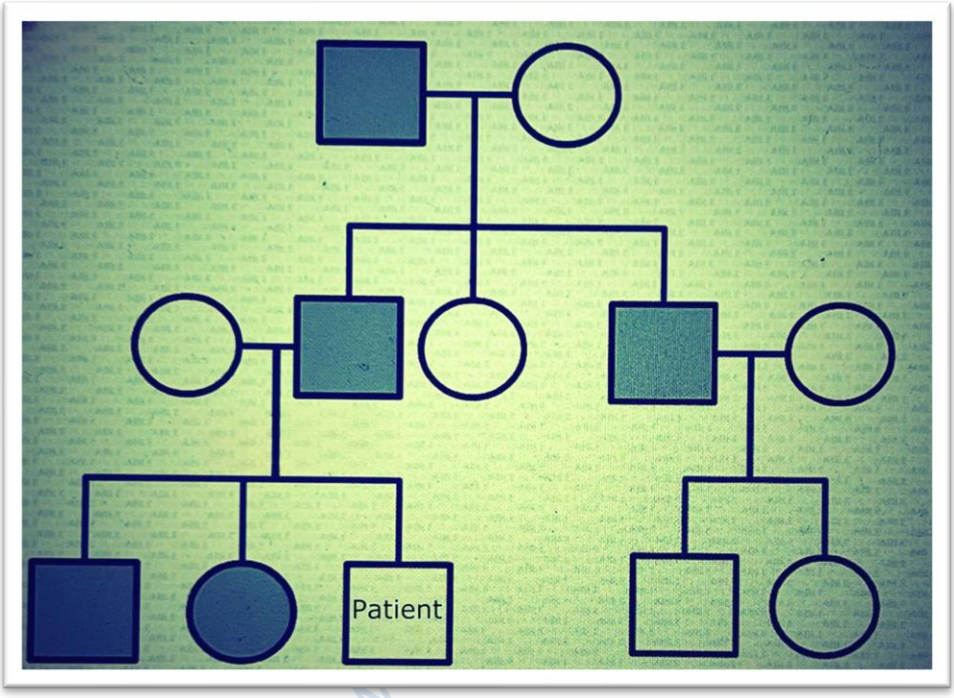
◙ **Examples of Autosomal Dominant Conditions:**

Huntington's Disease, Neurofibromatosis, Autosomal Dominant Polycystic Kidney Disease (ADPKD), BRCA gene (breast cancer), VWD, Hereditary spherocytosis.

Key 52

Knowing that the father, sister, and brother had experienced episodes of malignant hyperthermia following general anaesthesia. The following

pedigree shows the malignant hyperthermia among the family. What is the mode of inheritance?



√ This pedigree shows → **Autosomal dominant** pattern.

√ Note that in each generation, there is **at least 50%** affected people.

√ Also, be aware that **malignant hyperthermia** is an autosomal dominant condition.

◙ **Remember:**

• **Square** = Male. • **Circle** = Female. • **Shaded squares or circles** = affected individuals.

• **Half-shaded squares or circles** = carriers.

	• **The line that crosses over a square or a circle** = dead "deceased". • **The arrow** or the word "**patient**" or "**P**" = the person who attended the clinic to seek information about his genetic condition "Proband = the starting point of the genetic study".
Key 53	**Scenario On Sickle Cell Anemia Genetics:** **A 29-year-old woman who is 8 weeks pregnant attends the antenatal clinic for the first time with her husband who has sickle cell anemia. She is unaware of her sickle cell status. She is from West Africa. What is the most appropriate initial investigation to assess the risk of their unborn child inheriting sickle cell anemia?** → **Maternal haemoglobinopathy screening.** • Since the father has sickle cell anemia (known). And the mother's status of the disease is unknow (and she is African) ↑ risk. → Assessing the mother's carrier status of sickle cell disease is crucial. • Maternal haemoglobinopathy screening will determine: √ If she is a carrier of sickle cell trait → significant risk for the child to inherit sickle cell disease.

	√ If she is not a carrier → the child "may" inherit the sickle cell trait, but will not develop the disease.
Key 54	**Diagnostic Test for Chromosomal Abnormalities During Pregnancy** **Scenario:** A 36-year-old woman, gravida 3 para 2, at 18 weeks gestation is concerned about chromosomal abnormalities due to a family history of Edwards syndrome (Trisomy 18). She has not undergone any prenatal screening tests. **Question:** What is the most appropriate investigation to confirm the presence of Edwards syndrome? **Options:** A. Chorionic villus sampling (CVS). B. Doppler ultrasound of the umbilical artery. C. Amniocentesis. D. Detailed ultrasound scan at 20 weeks gestation. E. Foetal echocardiography. **Answer → C. Amniocentesis.** **Explanation:**

	• **Chorionic villus sampling (CVS)** (performed between 11-14 weeks) is less suitable at 18 weeks. • **Amniocentesis** (performed between 15-20 weeks) is the most appropriate diagnostic test at this stage, providing a definitive analysis of fetal chromosomes. • **Doppler ultrasound of the umbilical artery** and **Foetal echocardiography** are not diagnostic for chromosomal abnormalities. • **Detailed ultrasound at 20 weeks** can identify physical abnormalities but does not confirm chromosomal conditions. **Remember, For Fetal Karyotyping:** ◙ **Before pregnancy → Preimplantation Genetic Diagnosis (PGD).** ◙ **11-14 Week gestation → Chorionic Villous Sampling.** ◙ **15-20 Week gestation → Amniocentesis.**
Key 55	A 37-year-old man is concerned about the genetic risks for his children. He explains that his paternal grandmother had medullary thyroid carcinoma and passed away in his fifties. Additionally, his father has recently been diagnosed with hyperparathyroidism, and his paternal uncle has had a pheochromocytoma. He is worried about inheriting this genetic condition and the possibility of passing it on to his children. What is the most likely inheritance pattern of this condition?

Options:

A) Autosomal dominant.

B) Autosomal recessive.

C) X-linked dominant.

D) X-linked recessive.

E) Mitochondrial inheritance.

Answer:

Correct answer → A) Autosomal dominant.

This family history is suggestive of **Multiple Endocrine Neoplasia type 2 (MEN 2)**, an autosomal dominant condition. MEN 2 is characterised by the presence of **medullary thyroid carcinoma**, **hyperparathyroidism**, and **pheochromocytoma**, as described in the family. The **autosomal dominant inheritance pattern** means that each child of an affected parent has a **50% chance** of inheriting the condition.
